Remarks

Amendments to the specification describe individual parts of the revised drawings. A sequence listing is provided as a text file. Please use it as both the paper and the computer readable form of the sequence listing. These amendments introduce no new matter.

New claims 25-28 are supported at, *e.g.,* page 7, lines 11-6.

All prior rejections have been withdrawn and a new set of rejections are addressed below.

The rejection of claims 1-24 under 35 U.S.C. § 112, first paragraph

Claims 1-24 are rejected as failing to comply with the written description requirement. In particular, the terms "toxin defective" and "all or part of a toxin gene of a wild-type" were allegedly not described adequately. These are described as generic terms and there is allegedly no showing that applicants were in possession of the genus. Allegedly, "the disclosure fails to describe the common attributes or characteristics that identify members of the genus."

This allegation is respectfully traversed. The specification does describe the common attributes or characteristics of members of the genus. The prior art teaches three such toxin defective anaerobic bacteria in Dang, L. H., Bettegowda, C., Huso, D. L., Kinzler, K. W., and Vogelstein, B. (2001). Combination bacteriolytic therapy for the treatment of experimental tumors. Proc Natl Acad Sci U S A *27*, 27. These particular toxin defective bacteria were made by curing of a plasmid. Of 400 screened, three were observed to have lost the toxin gene. Thus it is not difficult or rare to make such toxin defective bacteria. Other ways to delete or mutate a toxin gene are known in the art. Ways for testing for a loss in toxicity of a bacterium are known in the art. Given the predictability of this type of basic bacterial mutagenesis, the genus is adequately described.

The specification teaches:

> Decreasing the natural production of toxins is desirable in using bacteria therapeutically. While toxin-defective strains need not be totally non-

> toxigenic, it is desirable that at least one of the toxin genes by [*sic*] mutated, deleted, or otherwise inactivated to render the bacteria less harmful to the host. Preferably the toxicity is reduced by a factor of at least 2, 5, 10, 50, 100, or 1000. If a toxin gene is episomal or on a phage, then curing of the episome or phage can be used to delete the toxin gene. Techniques are well known in the art for mutagenesis, curing, and screening of mutants.

Page 7, second full paragraph. Toxin defective bacteria are well known in the art. See for example, Analysis of the pathogenicity locus in *Clostridium difficile* strains. Cohen SH, Tang YJ, Silva J Jr. J Infect Dis. 2000 Feb;181(2):659-63. No more should be necessary to adequately describe them.

The rejection of claims 1-24 under 35 U.S.C. § 112, first paragraph

Claims 1-24 stand rejected as not enabling for bacteria other than Clostridium novyi-NT strain. As discussed above, methods for making toxin-decreased mutations and curing of plasmids and phage were well known in the art. The NT strain was not the only one known in the art. Others are taught in, for example, Dang, 2001 and Cohen 2000. It would require only routine experimentation for one of skill in the art to make additional mutations. No undue experimentation would be required. The techniques for making mutations, curing plasmids, and testing for toxicity were well known in the art. The Wands factors when properly considered and balanced should lead to a conclusion of enablement. This portion of the invention (this is not the invention *per se*) is already taught in the prior art. A number of such toxin-defective anaerobic bacterial strains were known. The techniques for making and identifying them were known. The predictability was high. The state of the prior art and the skill of those in the art was high.

The Office Action supports its rejection with a statement from Dang et al. that states that dramatic effects on large tumors were seen with C. novyi-NT spores, dolastatin-10, and MMC, but rarely with the spores alone. This statement does not relate to the toxin production of bacteria. This statement reports that for large tumors, more than just spores, but also drugs were necessary to obtain dramatic effects. This simply does not speak to the amount of experimentation that might be required to find a toxin-defective anaerobic bacterium.

In addition, applicants direct the examiner's attention to a table in the Dang patent U.S. 7,344,710. At column 7, Table 1 lists all the bacterial strains that were tested. Among the strains

tested, two were found to exhibit extensive spreading throughout the poorly vascularized portions of the tumors. These were selected for further study. There is no indication that the others were totally unsuitable, only that the two selected may be more effective in the spreading through large tumors.

It is respectfully submitted that one of ordinary skill in the art could make toxin-defective strains of anaerobic spore-forming bacteria without recourse to undue experimentation. Please withdraw this rejection.

The rejection of claims 1-24 under 35 U.S.C. § 112, first paragraph

Claims 1-24 stand rejected as not enabled because of an alleged need for a deposit to enable a microorganism. This rejection is respectfully traversed.

The premise of this rejection is entwined with the prior rejection. If the genus of recited bacteria is enabled, as urged above, then the particular strain that was used in the working examples is not necessary for enablement. The strain is just one of many strains which one of skill in the art could make. See the Dang (2001) and Cohen (2000) references. The *C. novyi-NT* strain is not necessary for practicing the invention and is not recited in any claim. Therefore, a deposit of this particular strain should not be necessary.

Many starting strains are disclosed in Dang U.S. 7344710 which were obtained from the ATCC. See Table 1. These twenty-five strains are all publicly available. As urged above, it is well within the skill of the art to cure an episome or phage carrying a toxin gene. It is well within the skill of the art to mutagenize a toxin gene. It is well within the skill in the art to test for loss of toxicity. Obtaining a strain for use in the claimed invention would not require undue experimentation. The claims are therefore enabled without a deposited microorganism.

Please withdraw this rejection in view of the enablement of the methods.

The rejection of claims 1-24 under 35 U.S.C. § 103(a)

Claims 1-24 stand rejected as obvious over Dang U.S. 7,344,710 in view of Fojo (Current Opinion, 2000), Helson (U.S. 5,688,517) and Dewhirst (U.S. 5,554,638). This rejection is respectfully traversed.

Claims are drawn to a method for treating tumors in a mammal and a kit for treating tumors. The method comprises administering to the mammal spores of a toxin-defective, anaerobic bacterium and administering to the mammal a microtubule stabilizing antitumor agent, whereby the tumor regresses or its growth is slowed or arrested. The kit for treating tumors has components that are in a divided or undivided container, wherein the components are the spores of the bacterium and a microtubule-stabilizing anti-tumor agent. The bacterium may optionally be *Clostridium novyi* or *Clostridium sordellii*. The kit may optionally further comprise a nitric oxide synthetase (NOS) inhibitor. The microtubule-stabilizing anti-tumor agent may optionally be taxol, taxotere, cephalomannine, epothilone B, or taxane. The method recites administering steps which may optionally be performed serially and may optionally be done intravenously or intratumorally.[1]

Dang teaches a method (and kits) for treating tumors in which spores of anaerobic, toxin-defective bacteria are administered to a patient with a tumor. In addition, Dang teaches administering an anti-tumor agent which can be a DNA damaging agent, agents that collapse tumor vasculature, radiation, and anti-tumor antigen antibodies. Column 4, lines 34-41. Suitable anti-tumor agents which function to collapse tumor vessels are vinblastine, vincristine, colchicine, combrestatin A-4, dolastatin-10, and 5, 6, dimethylxanthenone-4-acetic acid. Column 4, lines 59-62. Dang further teaches that among the agents that collapse tumor vasculature were microtubule binding agents. "The latter class of agents has been shown to be able to interfere with proper circulation through the tumors and thereby trap large molecules, such as antibodies or bacteria, that have gained access to the tumor tissue." Column 9, lines 1-4. Dang further teaches, "Presumably the vascular collapse further lowered the oxygen tension near the trapped bacteria and thereby increased the potential for bacterial growth." Column 9, lines 25-28. Thus Dang teaches that the useful drugs for combination with the bacterial spores that provide synergistic killing were agents which destabilized the microtubules, causing the collapse of the tumor vasculature.

In contrast, the claimed invention utilizes agents which have the diametrically opposite effect, *i.e.,* they are microtubule stabilizing agents.

[1] Recitations of dependent claims are not required in the independent claims from which they depend.

Fojo is cited as teaching microtubule stabilizing agents such as taxane, taxotere, taxol, taxane, and epothilone B for treating tumors. Helson is cited as teaching cephalomannine for treating tumors. Dewhirst is cited as teaching NOS inhibitors for treating tumors.

The Office Action asserts that it would have been obvious to substitute the microtubule destabilizing agents of Dang with the microtubule stabilizing agents of the Fojo and Helson, because they were all known to have anti-tumor effect. Moreover, the Office Action asserts that stabilizing agents suppress microtubule dynamics without increasing in polymer mass or formation of microtubule bundles. Finally, the Office Action asserts that one of skill in the art would have known that microtubule stabilizing agents would provide successful results.

The MPEP teaches that the proposed modification of a reference cannot change the principle of operation of a reference. § 2143.01. The MPEP guides:

> If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959) (Claims were directed to an oil seal comprising a bore engaging portion with outwardly biased resilient spring fingers inserted in a resilient sealing member. The primary reference relied upon in a rejection based on a combination of references disclosed an oil seal wherein the bore engaging portion was reinforced by a cylindrical sheet metal casing. Patentee taught the device required rigidity for operation, whereas the claimed invention required resiliency. The court reversed the rejection holding the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate." 270 F.2d at 813, 123 USPQ at 352.).

In the present application, the rejection proposes that the primary reference Dang, be modified so that a microtubule ***destabilizing*** agent is replaced with a microtubule ***stabilizing*** agent. However, as the MPEP analyzes, this would require a change in the basic principle under which the Dang reference was designed to operate. It cannot be obvious to use a class of agents that have the opposite effect from those that are taught in the prior art. The Dang reference constitutes a teaching away from using a microtubule stabilizing agent in combination with the bacterial spores.

Therefore, the combination of references is improper and a *prima facie* case of obviousness has not been made. Withdrawal of the rejection is therefore respectfully requested.

The rejection of claims 1-15 under the judicial doctrine of obviousness-type double patenting

Claims 1-15 stand rejected for double patenting as non-statutorily obvious over claims 1-5 and claim 20 of Dang, U.S. 7344710 in view of Fojo, Helson, and Dewhirst. This rejection is respectfully traversed.

The teachings of Dang have been discussed above. Claims 1and 2 are directed to the administration of toxin-defective spores of *Clostridium novyi* and *Clostridium sordelli*, respectively. Claim 3 is directed to the use of a combination of such spores and an anti-tumor agent. Claims 4, 5, and 20 are dependent on claim 3. These claims are generic to the subject claims which recite use of such spores and microtubule stabilizing anti-tumor drugs.

Claims 6 and 7 recite using different anti-tumor agents, particularly radiation and an antibody. These claims are not generic to the subject claims.

Claims 8-15 recite using an anti-tumor agent which collapses tumor vasculature. These claims are not generic and additionally are mutually exclusive to the claimed invention.

The subject claims are directed to a species of the generic claims which employ an anti-tumor agent in combination with spores. The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird,* 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."). MPEP § 2144.08.

Specifically with regard to double patenting, the MPEP cautions: Domination and double patenting should not be confused. They are two separate issues. One patent or application "dominates" a second patent or application when the first patent or application has a broad or generic claim which fully encompasses or reads on an invention defined in a narrower or more specific claim in another patent or application. Domination by itself, *i.e.,* in the absence of statutory or nonstatutory double patenting grounds, cannot support a double patenting rejection. *In*

re Kaplan, 789 F.2d 1574, 1577-78, 229 USPQ 678, 681 (Fed. Cir. 1986); and *In re Sarrett*, 327 F.2d 1005, 1014-15, 140 USPQ 474, 482 (CCPA 1964).

As discussed above, the subject claims are not obvious in view of the combined teachings of Dang and the other references because the art taught that microtubule ***destabilizing*** agents were highly desirable agents for combining with the bacterial spores. This is an implicit teaching away from using microtubule ***stabilizing*** agents. Contrary to the assertion of the rejection, based on a reading of the teachings of the entire prior art, one of skill in the art would not have expected successful results and would not have been motivated to select microtubule stabilizing agents. The Dang reference (and the scientific publication of the same work) teaches that the highly favorable results that they observed were based on the ***destabilization*** of microtubules. One of skill in the art would therefore have been led away from the invention and would not have expected success.

Withdrawal of this rejection is respectfully requested as it would not have been obvious to combine the prior art teachings of the secondary references with Dang's claimed invention of claims 1-15 and 20.

Conclusion

A speedy allowance of all claims is requested, as the prior art neither taught nor suggested the combinations as claimed, either as a method of treating or as a kit for treating tumors.

Respectfully submitted,

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